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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/691,654	10/24/2003	Tomoko Maeda	244295US0CONT	1300
22850	7590	11/23/2005	EXAMINER	
OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.			AFREMOVA, VERA	
1940 DUKE STREET			ART UNIT	
ALEXANDRIA, VA 22314			PAPER NUMBER	

1651

DATE MAILED: 11/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/691,654	MAEDA ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21,22 and 25-44 is/are pending in the application.
- 4a) Of the above claim(s) 26-41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21,22,25 and 42-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/646,859.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 21, 22, and 25 as amended (9/08/2005) and new claims 42-44 (9/08/2005) are under examination in the instant office action.

Claims 1-20, 23 and 24 are canceled.

Claims 26-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

Claim Rejections - 35 USC § 112

New claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation "the cells". There is insufficient antecedent basis for this limitation because there are several "cells" including blood cells, osteoclast precursors cells, "non-adherent" and "obtained cells" in the method of preceding claim 42. Thus, it is uncertain what cells are cultured for 1-3 weeks.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 22 and 25 as amended are rejected under 35 U.S.C. 102(b) as being anticipated by Dahl et al. (IDS reference; Annals of the Rheumatic Diseases. 1985, Vol. 44, pages 647-657).

Claims are directed to a method for producing osteoclast precursor cells wherein the method comprises step of obtaining a cellular fraction containing granulocytes and lymphocytes from joint fluid by centrifugation and subsequently culturing the cells in an essential medium for mammalian cells in the presence of serum and in the absence of additional cytokines. Some claims are further drawn to culturing cells at 35-37 degree C in 5% carbon dioxide containing air for 1-3 weeks.

Dahl et al. discloses a method for culturing and manipulating cells derived from synovial specimens of joints of patients with rheumatoid arthritis (page 649, column 1) wherein the method comprises steps of obtaining cells from synovial cavity by centrifugation to eliminate dead cells and cell debris (page 649, col.1, par. 3, lines 18-20) and subsequently culturing the cells in an essential medium for mammalian cells RPMI in the presence of serum and in the absence of additional cytokines (page 649, col. 1, par. 4, lines 1-2). The reference by Dahl et al describes that synovial cavity contains various cells including lymphocytes, granulocytes, macrophages (page 647, col. 1, par. 1). Thus, the starting cellular fraction is the same as required by the claimed method. The cells are cultured cells at 37 degree C in 5% carbon dioxide containing air for a total period of about a week (48 hours plus 84 hours; see paragraph bridging col. 1 and col. 2 on page 6549). Thus, the disclosed method comprises identical steps of culturing identical cells at identical conditions as required by the claimed method and, therefore, the intended results or effects are reasonably expected to be identical including results/effects of producing osteoclast precursor cells.

Moreover, the reference by Matayoshi et al. (IDS reference; Proc. Natl. Acad. Sci. USA. 1996, Vol. 93, pages 10785-10790) teaches that precursors of osteoclasts are derived from

Art Unit: 1651

monocyte-macrophage lineage cells (page 10785, col. 1, par. 1) and the cited reference by Dahl et al describes that synovial cavity contains cells of monocyte-macrophage lineage including lymphocytes, granulocytes and macrophages. Therefore, osteoclast precursor cells are found in synovial specimens or in synovial fluids of joints.

Thus, the cited reference by Dahl et al. is considered to anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

New claims 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Purton et al. (IDS reference; Blood. 1996, Vol. 87, NO. 5, pages 1802-1808) taken with Pollice et al. (Journal of Orthopaedic Research. 1995, 13:325-334).

Claims are directed to a method for producing osteoclast precursor cells wherein the method comprises step of obtaining peripheral blood mononuclear cells (PBMCs) by centrifugation, step of culturing the cells in essential medium for mammalian cells in the absence of additional cytokines for 1-2 hours, step of rinsing out non-adherent cells, and step of culturing the obtained cells in the absence of additional cytokines 1-3 weeks. Some claims are further drawn to incorporation of serum in the medium and to culture conditions including 35-37 C in 5% carbon dioxide containing air for 1-3 weeks.

Purton et al. disclose a method for producing osteoclast precursor cells wherein the method comprises step of obtaining peripheral blood mononuclear cells by centrifugation (page

Art Unit: 1651

1802, col.2, par. 3), culturing peripheral blood derived cells in essential medium for mammalian cells MEM supplemented with serum and in the absence of cytokines at 35-37 C in 5% carbon dioxide containing air (page 1802, col. 2, last par. and page 1803, col. 1, line 3) for 14-21 days or for 1-3 weeks (see abstract). The TRAP-positive osteoclast precursor cells have been found/demonstrated after 14-21 days of culturing both normal peripheral blood monocytes and mobilized peripheral blood monocytes (page 1806, col. 1, par. 3). Purton et al. clearly teaches that TRAP staining of adherent cells reveals that many mononuclear precursors and multinucleated cells are TRAP-positive (Fig. 3, page 1804). The TRAP positive mononuclear precursors are the precursors of osteoclasts.

The cited reference by Purton et al. teaches that TRAP-positive precursors of osteoclasts are found within population of adherent cells. But the culturing protocol for producing osteoclast precursor cells as described by Purton et al. does not comprise step of eliminating non-adherent cells after 1-2 hours of cell culturing in the medium.

However, the reference by Pollice et al. teaches that 2-hour cell preplating or removal of non-adherent cells after incubation for 2 hours decreases the number of TRAP negative cells in population of mononuclear cells derived from bone marrow as intended for isolation and for producing osteoclast precursor cells (page 328, col.1, last 4 lines).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the Purton's protocol by adding step of removal of non-adherent cells after 1-2 hours of incubation with a reasonable expectation of success in producing osteoclast precursor cells because TRAP-positive preosteoclast cells are found in adherent cell populations as taught by Purton and because TRAP-negative cell numbers are

Art Unit: 1651

decreased by preplating and/or removal of adherent t cells after 1-2 hour of incubation of starting mononuclear cell populations as taught by Pollice et al. One of skill in the art would have been motivated to remove or to rinse out the non-adherent cells in order to decrease amounts of TRAP-negative cells and, thus, at the very least to relatively increase numbers of TRAP-positive cells including osteoclast precursors in mixed mononuclear cell populations for the expected benefits in maximizing detection and yield of TRAP-positive osteoclast precursors. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 9/08/2005 have been fully considered. Applicant's arguments with respect to amended and new claims have been considered but they are not found persuasive. Some arguments are moot in view of the new ground(s) of rejection.

Claim rejection under 35 U.S.C. 102(b) as being anticipated by Purton et al. (IDS reference; Blood. 1996, Vol. 87, NO. 5, pages 1802-1808) have been withdrawn because Purton et al. does not describe step of eliminating non-adherent cells after 1-2 hours of cell culturing in the medium. In the method of Purton non-adherent cells are removed after 3 days of culturing. Applicants appear to argue that the method of Purton results in production of osteoclasts but not in production of preosteoclasts because cells are TRAP-positive. However, accordingly to the applicants' definitions preosteoclasts and osteoclasts are both TRAP-positive cells (page 19,

Art Unit: 1651

lines 14-17). The cited reference by Purton clearly acknowledged the distinction between 2 types of cells such as TRAP-positive mononuclear precursor cells (preosteoclasts) and TRAP-positive multinucleated cells (osteoclasts) in the discussion of results of culturing protocols (FIG. 3, page 11804).

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

Art Unit: 1651

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651

November 21, 2005

A handwritten signature in black ink, appearing to read 'V. Afremova', with a stylized, flowing script.

VERA AFREMOVA

PRIMARY EXAMINER